Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs in athletes

G Lippi, M Franchini, G C Guidi

Aspirin and the non-steroidal anti-inflammatory drugs (NSAIDs) have been commercially available for decades, and their ability to reduce pain and inflammation is well established. It was first shown nearly 30 years ago that aspirin strongly inhibits platelet function by acetylation of platelet cyclo-oxygenase (COX) at the functionally important amino acid serine 529. This prevents access of the substrate (arachidonic aid) to the catalytic site of the enzyme at tyrosine 385 and results in irreversible inhibition of platelet dependent formation of thromboxane, a powerful promoter of aggregation, for the lifetime of the platelet (7–10 days). Aspirin is about 150–200-fold more potent as an inhibitor of the constitutive isoform of the platelet enzyme (COX-1) than the inducible isoform (COX-2), which is expressed by cytokines, inflammatory stimuli, and some growth factors.[1] This explains the different dose requirements of aspirin as an antithrombotic (COX-1) and an anti-inflammatory drug (COX-2).[2] Non-aspirin NSAIDs inhibit the activity of both COX-1 and COX-2 by reversibly blocking the access of arachidonic acid to the active site at the apex of a hydrophobic channel within these enzymes.[1] Acetaminophen is a weak, non-selective inhibitor of both COX enzymes, although the precise mechanism of action remains elusive. It has been recently proposed that it might act to reduce the active, oxidised form of both the COX enzymes, which would make it more potent at sites that have low peroxide concentrations, such as the brain and spinal cord.[3] Aspirin and NSAIDs are non-selective inhibitors of both COX-1 and COX-2, whereas newer agents termed ''coxibs'' are selective inhibitors of COX-2.[4] The identification of COX-2 selective inhibitory NSAIDs was thought to be a major breakthrough, with the expectation of a significant reduction in side effects. The major controversy with respect to the COX-2 selective inhibitors as a class has been the increase in myocardial infarction and other cardiovascular events observed in some studies. Thus the initial expected global benefits of the COX-2 selective inhibitors may be outweighed by their potential for toxicity.[5]

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Regardless of their preventive and therapeutic efficacy in chronic inflammatory pathologies, NSAIDs are currently prescribed for a variety of additional disorders.[6] Owing to its inhibitory effects on platelet function, aspirin is currently used in primary and secondary prevention of cardiovascular disease, namely acute myocardial infarction and acute occlusive stroke.[7] NSAIDs are also drugs of choice for pain and inflammation management, because of the integrated role of the COX pathway in the generation of inflammation and in the biochemical recognition of pain.[5] Evidence supports the use of a variety of NSAIDs for migraine prevention.[8] Pain is one of the most common reasons patients seek dental treatment, and NSAIDs provide excellent relief through their anti-inflammatory and analgesic actions.[9] Regardless of these generic indications, the use of NSAIDs is commonplace in athletes.[10 11] NSAIDs were the most commonly used drugs in Canadian athletes who participated at both the Atlanta and Sydney Olympics.[12] NSAIDs are widely used by athletes to treat banal disorders such as cold, flu, and moderate pain, to improve healing time, and to alleviate pain, swelling, and disability associated with injury or contusions, decreasing the amount of time missed from sports competition.[13 14] However, the adverse consequences and the side effects of these drugs are often underestimated.

NSAIDs can cause several clinically meaningful adverse effects. By inhibiting the key COX enzyme in prostaglandin synthesis, aspirin-like drugs prevent the production of physiologically important prostaglandins that protect the stomach mucosa from damage by hydrochloric acid, maintain kidney function, and aggregate platelets when required. Thus the chief side effects range from gastric injury to gastric ulceration and renal damage.[6] Incorporation of a nitric oxide generating moiety into the molecule of NSAIDs was shown to attenuate their ulcerogenic activity, although several findings suggest a possible involvement of NO in the pathogenesis of arthritis and tissue destruction.[15] Therefore, because of the inhibition of platelet function, any effective NSAID dose is associated with an increased risk of bleeding.[2] NSAIDs increase the risk of developing intracranial haemorrhage after minor head injury.[16] Moreover, patients taking aspirin before emergency fixation of bone fractures have a significantly lower haemoglobin concentration and packed cell volume and are more likely to be anaemic at presentation.[17] This has been clearly established for aspirin, but there is growing evidence of an increased risk of ulcers and bleeding in patients taking acetaminophen.[18] Thus current scientific evidence strongly supports careful consideration before administering aspirin and other NSAIDs to athletes who are engaged in contact sports or other sport disciplines that put them at major risk of traumatic injuries, such as motor racing and downhill skiing, as these drugs have the potential to seriously exacerbate post-traumatic haemorrhagic complications.[19] Alleviation of the ''alarm system'' of pain from the onset of a sport injury by the use of NSAIDs may also place the athlete in jeopardy with respect to tissue overload and failure.[20] Finally, recommendations should be made to prohibit athletes from participating in risky sports disciplines once NSAIDs need to be administered.

Millions of people world wide are regularly taking analgesic and anti-inflammatory drugs for banal disorders, as they are effective in relieving both pain and inflammation, with little awareness of safety, tolerability, risks, and potential adverse complications.[1] An individual benefit/risk ratio should be carefully determined before administration of NSAIDs, especially in athletes who are at major risk of traumatic injury. Thus, when prescribing NSAIDs for athletes, doctors should consider not only their efficacy, but also their toxicity and bleeding risks, as recently highlighted by the Third Canadian Consensus Conference, which recommended routine reassessment of a patient's risk before prescribing NSAIDs, regardless of the individual lifestyle.[21]

Future studies are needed to address the many important and unanswered questions on the bleeding effects of the

different analgesic and anti-inflammatory drugs in athletes, providing specific expert recommendations on this topic. There is already an ongoing, randomised controlled trial in Canada, aimed at modifying prescription of easily accessible, over the counter NSAIDs for patients requiring chronic treatment.[22] It is to be hoped that similar educational policies will be extended to sports physicians and athletes, otherwise the considerable efforts to ensure the health of athletes by preventing injuries and related complications—for example, mandatory wearing of helmets in professional cycling or HANS carbon fibre collars by professional drivers[23 24]—will be wasted.

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COMMENTARY

The article as written addresses the need and desire to treat musculoskeletal pain induced by sport activities. However, there is a clear need to explore the benefits and side effects of available analgesics, in this case the NSAIDs. To date, guidelines expressed in the musculoskeletal literature have been unhelpful and misleading. In the early 1990s, acetaminophen (paracetamol) was recommended in guidelines as the first choice analgesic for osteoarthritis by academic advisory bodies such as the British Society for Rheumatology with the Royal College of Physicians (UK)[1] and the American College of Rheumatology (ACR).[2 3] This was an attempt to facilitate a uniform approach to the clinical management of osteoarthritis, and to attempt to reduce toxicity exposure to NSAIDs. However, it must be noted that guidelines provide explicit recommendations, and seek to influence practice using a formal process to disseminate advice on the most efficacious management, in the light of scientific evidence, but are not intended to replace clinical judgment. Although the UK and ACR guidelines had good attributes, both advocated the use of acetaminophen as the drug of first choice in the treatment of osteoarthritis, this despite the fact that osteoarthritis is a painful inflammatory condition. The UK and ACR guidelines' committees referred to a study by Bradley *et al*[4] and relied heavily on this as ''good'' evidence that acetaminophen was equally as effective as ibuprofen in the management of osteoarthritis. The study of Bradley and colleagues was underpowered and suffered from selection bias and author reporting bias on a non-uniform group of patients. In addition, it has been shown that the relative risk of gastrointestinal bleeding with acetaminophen is significant and equivalent to many NSAIDs.

The more recent Canadian guidelines[5] on the use of NSAIDs add little to the clinician's armamentarium, while still retaining COX-2 selective inhibitors as an option, but merely advising the clinician to use their own judgment in the final prescribing process. The biochemical identification of COX-2, and the subsequent introduction of the selective COX-2 inhibitor NSAIDs, was thought to be a major breakthrough in clinical pain management with the hope of good clinical efficacy in the treatment of musculoskeletal disorders and the expectation of a significant reduction in gastrointestinal side effects.[6] It was subsequently established that celecoxib did not have fewer gastrointestinal side effects than traditional NSAIDs, and the reduction in gastrointestinal symptomatic problems for the COX-2 selective inhibitors in general versus traditional NSAIDs is modest.[7 8] In addition, there is no evidence that the COX-2 selective inhibitors are clinically more effective than the traditional NSAIDs.[8 9] Thus notwithstanding the cardiovascular side effects of the COX-2 selective inhibitors, there does not appear to be any clinical advantage to prescribing a COX-2 selective inhibitor over a traditional NSAID. Furthermore, it should be noted that a large proportion of the population over the age of 50 need acetylsalicylic acid for cardiovascular protection. The use of acetylsalicylic acid with a COX-2